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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/637,710	PANDA ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed on January 8, 2007 has been received and entered. Claims 2-3, 6 and 8-21 has been canceled, while claims 1, 4, 5 and 7 have been amended.

Election/Restrictions

Applicant's election of invention of claims 1-8 (group I) in the reply filed on May 2, 2006 was acknowledged. Because applicant did not specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse (MPEP § 818.03(a)).

Claims 1, 4-5 and 7 are under consideration in the instant application.

Withdrawn-Claim Objections

The objection to claim 3 as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn in view of cancellation of the claim.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 8, line 15. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 4-5 and 7 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

Claims 1, 4-5 and 7 are directed to a transgenic knockout mouse whose genome comprises a disruption in each allele of the mouse's endogenous melanopsin gene, wherein disruption in each allele prevents the expression of a functional melanopsin protein in cells of the mouse and the mouse exhibits an attenuated circadian rhythm phase shift in response to a light pulse during a dark portion of an environmental dark/light cycle. Claim 4 is directed to cell isolated from the transgenic knockout mouse of the invention. Claim 5 is directed to a method of identifying a therapeutic agent for modulating circadian rhythm disorder in any mammal. In the instant case, claimed transgenic mouse is not supported by either a specific and substantial asserted utility or a well-established utility because the specification fails to assert any specific and substantial asserted utility for the claimed transgenic mouse.

The specification teaches a transgenic mouse comprising a disruption in the melanopsin gene as well as methods for using the animals to identify agents useful for modulating circadian rhythm in animals (see abstract). The disclosure states identification of the photoreceptors that communicate light information to the clock is difficult and studies have indicated that photoentrainment of circadian rhythms can occur in the absence of classical visual photoreceptors, rods and cones (see page 2, para. 6). The invention embraces a knockout whose genome comprises a homozygous disruption in the mouse's endogenous melanopsin gene resulting in prevention of expression of a functional melanopsin protein in cells of the mouse. In some embodiments, the mouse comprises a disruption of the melanopsin gene exhibiting an attenuated circadian rhythm phase-shift in response to a light pulse during a dark portion of an environmental dark/light cycle (see page 3, para. 8 and 9). The

specification contemplate transgenic animals are useful in identifying a therapeutic agent for modulating circadian rhythm in a mammal (see page 3 paragraph 10). It is noted that neither specification nor art of record discloses that instant transgenic mouse phenotype is associated with any disease condition or model for any disorder. The specification teaches melanopsin knockout mice showing no immunostaining for melanopsin in Opn4-/- mice while Opn4+/+ and Opn4+/- mice show anti-melanopsin immunoreactive. It is further noted that Opn4-/- mice show no detectable defect in locomotor activity rhythms when placed in constant darkness (Figure 2 A and B). These mice show a significantly attenuated phase delay in comparison to the wild type animals (Figure 3). It is noted that the phase delay was significant at sub saturating irradiance of light, while only a slight attenuation of the phase shift was seen at higher irradiance in the knockout animals (pages 28-30 pf the specification). It is further noted that the instant specification contemplates modulator of circadian rhythm on transgenic knockout animals are useful for preventing or treating a number of conditions by specifically advancing or delaying the phase of certain circadian rhythms in humans. The test agents would be useful in condition including to achieve chronobiologic effects and/or to alleviate circadian rhythm phase disturbances in subjects, insomnia, seasonal sffective disorder (SAD), shift work dysrhythmia, delayed-sleep phase syndrome, Irregular Sleep/Wake Pattern, advanced sleep phase syndrome, non-24-hour sleep/wake syndrome, and time zone change syndrome. In addition, the modulators can be administered to, a person who live in darkness; those suffering from winter depression, or other forms of depression; the aged; Alzheimer's disease patients, or those suffering from other forms of dementia; or patients who require dosages of medication at appropriate times in the circadian cyclesbehaviors, and anxiety (see paragraph 54 of the specification). In addition, specification discloses alterations of response in the knockout mouse of the invention could indicate that the agent acts on a melanopsin-specific signal transduction pathway (see page 16, para 56). In the instant case, specification fails to disclose any asserted utility for the mouse as a model or for a method of identifying therapeutic agent that could explicitly indicates the role of

melanopsin in any of the disorder as mouse model that are found to be specific and/or substantial.

At the time of filing of instant application, an artisan would have not found such utilities evident because specification does not provide a correlation between a melanopsin gene and established function, phenotype or disease. The specification discloses no nexus between melanopsin gene and any known pathological state associated with condition set forth in paragraph 54 of the specification (supra). The specification contemplates that experiments show alterations of response in the knockout mouse can indicate that the agent acts on a melanopsin-specific signal transduction pathway (see page 16, para 56). At the time of filing of instant invention, Beault et al (J Mol Neuroscience. 2003; 21(1): 73-89, art of record) disclose melanopsin, in itself, is not necessary for circadian photoreception. In fact, Beault et al states, "it appears that of the known photoreceptor systems, none, in and of itself, is necessary for circadian photoreception. Instead, it appears that within the photoreceptive systems there is some degree of redundancy, each contributing in some way to photic entrainment" (abstract). It is not apparent how administration of agent to the transgenic knockout mouse the invention wherein melanopsin gene is deleted and shows no functional melanopsin protein would provide any information on melanopsin-specific signal transduction pathway. Kumbalasiri et al (Exp Eye Res. 2005; 81(4):368-75) while reviewing the state of melanopsin and other novel mammalian opsins describes that disruption of a given opsin gene may result in compensation by other opsins. Kumbalasiri et al emphasizes the use of more sophisticated inducible knockout strategies to study the roles of the members of this interesting class of photopigments (see page 373, col. 2, last para bridging to page 374). This is further supported by Holschneider et al. (Int J Devl Neuroscience, 2000, 18: 615-618, art of record) who describes that single genes are often essential in a number of different physiological processes. Hence, deletion of an individual gene may prove so drastic or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interaction of various new physiologic changes (pp 615). Holschneider et al discuss various factors that contribute to the resulting phenotype of transgenic mice, including

compensatory system that may be activated to mask the resulting phenotype; these compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene.

The specification of the instant application fails to provide any correlation between the disclosed phenotypes and function or role of melanopsin gene in any specific disease or any disorder. Thus, in order to determine the specific utility for the mice, the Artisan of skill would need to perform further research upon the claimed mice in order to determine the correlation between the knockouts and the observed phenotypes relating to genus of disorder as described in the specification (see page 15, para. 54 of the specification). It is noted that that the transgenic mouse of the invention shows a slight attenuation of the phase shift was seen at higher irradiance in the knockout animals (pages 28-30 pf the specification). The specification also discloses a melanopsin knockout mouse show attenuated circadian phase shift in response to light suggesting potential role of this gene in circadian rhythm related disorder. Therefore instant knockout and knock in animal can be used as model for genus of disorders to screen therapeutic that modulates circadian rhythm and have potential to treat condition such as depression, jet lag, Alzheimer's disease. However, neither the specification nor the art disclose any known specific relationship of deletion of melanopsin gene to any specific condition or disease. It is generally known in the art that any observed phenotype in homozygous disruption may be because of compensatory system that may be activated to mask the resulting phenotype. These compensatory changes may be due to differential expression of another gene, which may be regulated by the downstream product of the deleted gene (Holschneider et al. Int J Devl Neuroscience, 2000, 18: 615-618, page 615). It is emphasized that applicants do not provide any nexus between deletions of gene to any specific condition or disease that could be directly attributed to the deletion of the melanopsin gene. Thus, asserted utility of using the mice to identify drugs in any disease model is not substantial or creditable because specification does not identify any compound that could modulate circadian rhythm or discloses a mouse that shows abnormalities consistent with genus of disorders disclosed in the specification.

As set forth in the utility guideline a general statement of any specific utility, such as identifying a therapeutic agent for modulating circadian rhythm in mammal or genus of other related disorder or condition would ordinarily be insufficient. Similarly, a statement of utility for plurality of screening method is non-specific, renders the purported utility of the claimed knockout mice to be non-specific. The usefulness of the transgenic mice, as models for circadian rhythm related disease, is not clear, absence of assessment that they reflect a particular diseases state. This leaves the Artisan of skill to speculate the uses of the mice and methods as claimed. Under the utility guideline set forth above requirement for further research or experimentation renders the claimed invention as lacking in a specific or substantial utility. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real-world" context of use are considered substantial utilities. The evidence of record has not provided any other utility for the transgenic mice encompassed by the claims that are substantial and specific. Since the mice have no determined specific function, the relation to any disease or condition is unknown, and further, because the phenotypes in the transgenic knockout mice are not specific to any one disease or condition, the Artisan, at the time of filing, would not know how to use the mouse or any data resulting from using the mice. To make such a determination, the Artisan of skill would need to further research to mice, to determine if functions associated with melanopsin are present in the mice, and then identify disease or condition associated with the disclosed phenotype. The specific utilities cited in the disclosure require further research to establish whether deletion of melanopsin can be attributed to a particular function or utility. The invention of claims 1, 4, 5 and 7 provide no specific and substantial utility, since no function can be attributed to the transgenic mouse of the invention, the cells obtained from such mouse would also have no specific and substantial utility.

Claims 1, 4-5 and 7 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-5 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Claims 1 is a transgenic knockout mouse whose genome comprises a disruption in each allele of the mouse's endogenous melanopsin gene, wherein disruption in each

allele prevents the expression of a functional melanopsin protein in cells of the mouse and the mouse exhibits an attenuated circadian rhythm phase shift in response to a light pulse during a dark portion of an environmental dark/light cycle. Claim 4 is directed to cell isolated from the transgenic knockout mouse of the invention. Claim 5 is directed to a method of identifying a therapeutic agent for modulating circadian rhythm disorder in any mammal. Subsequent claims limit the method of claim 5 to include phenotype of the knockout animal showing an attenuated circadian rhythm phase-shift response and selecting step comprising an agent that enhances the animal's circadian rhythm phase-shift response. Claim 8 limits the transgenic animal to include a mouse.

Claim 1 embraces a transgenic knockout mouse whose genome comprises a disruption in the mouse's endogenous melanopsin gene, wherein the disruption prevents the expression of a functional melanopsin protein in cells of the mouse. Claims 1 and 4 do not recite any specific phenotype associated with the transgenic knockout mouse. The specification teaches melanopsin knockout mice showing no immunostaining for melanopsin in Opn4-/- mice while Opn4+/+ and Opn4+/- mice show anti-melanopsin immunoreactive. It is further noted that Opn4-/- mice show no detectable defect in locomotor activity rhythms when placed in constant darkness (Figure 2 A and B). However, these mice show a significantly attenuated phase delay in comparison to the wild type animals (Figure 3). It is noted that the phase delay was significant at sub saturating irradiance of light, while only a slight attenuation of the phase shift was seen at higher irradiance in the knockout animals (pages 28-30 pf the specification). The specification provides no evidence that a transgenic mouse carrying a homozygous disruption of melanopsin gene exhibit any specific phenotype that may be associated with any specific disorders, screening for agents capable of modulating circadian rythym as compared to a wild type mouse. The specification provides working examples and guidance relating to homozygous mice whose genome comprises disruption in melanopsin gene. The specification teaches a number of tests that were carried out on melanopsin-disrupted mice. The data as presented does not disclose a coherent picture of the function of melanopsin gene or any condition associated with melanopsin knockout. In absence of any specific phenotype linking the mouse to any

specific condition or disease, an artisan would not know whether slight attenuation of the phase shift is due to melanopsin gene knockout or it is because of other compensatory factors. The skilled artisan would have to perform undue experimentation to make use of the invention. Prior to instant invention, the art teaches the feasibility of creating a homozygous disruption of a targeted gene of interest and the creation of transgenic mouse containing the same. However, the art also teaches the resulting phenotype of a knockout mouse is exceedingly unpredictable. For example, Leonard (Immunological Reviews, 1995, 148: 98-114, art of record) discloses mice with disruption in the gc gene that was intended to be a model for X-linked severe combined immunodeficiency (XCIDS), but displays a variety of unexpected traits (Abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (pp 105, line 7). Griffiths (Microscopy Research and Technique 1998, 41: 344-358, art of record) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotype (pp 350, last paragraph). Furthermore, the state of the art suggests such unpredictability of phenotype is correlative to the genetic background of the knockout mouse. For example, Keri et al., (Proc Natl Acad Sci U S A. 2000; 97(1): 383-7, art of record) show that elevated levels of lutenizing hormone in transgenic can result in different reproductive system abnormalities including ovarian tumors. Schoonjans et al (Stem Cells, 2003; 21:90-97), for example state that the phenotype of gene-targeted mice is not only due to genetic alteration itself but also to the genetic background in which it is generated (pp93, discussion). Wolfer et al (Trends in Neuroscience, 2002, 25 (7): 336-340, art of record) describe the unpredictability of phenotype resulting from gene disruption can influenced by gene flanking the disrupted coding sequence and by the general genetic background of mouse strains, wherein congenic strains carrying the same null mutation can sometime show widely divergent phenotypes (pp 336, column 1-3). Thus, at the time of filing, it is evident from the art of record that the resulting phenotype of a homozygous and s knockout was considered unpredictable and the specification does not provide any evidence to suggest that attenuation of the phase

shift is specific to deletion of melanopsin. The guidance provided by the specification amounts to invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention.

Claims 5 and 7 embrace a method for identifying a therapeutic agent for modulating circadian rhythm in a mammal by administering an agent to a transgenic knockout animal whose genome comprises a homozygous disruption in its endogenous melanopsin gene, wherein the disruption prevents the expression of a functional melanopsin protein in cells of the animal. It is noted that speciation contemplates modulator of circadian rhythm on transgenic knockout animals are useful for preventing or treating a number of conditions including advancing or delaying the phase of certain circadian rhythms in humans, insomnia, delayed-sleep phase syndrome, Irregular Sleep/Wake Pattern, advanced sleep phase syndrome, time zone change syndrome, winter depression, or other forms of depression; Alzheimer's disease, dementia, and anxiety (see paragraph 54 of the specification). The specification discloses alterations of response in the knockout mouse of the invention could indicate that the agent acts on a melanopsin-specific signal transduction pathway. The disclosure provided guidance in terms of deletion of melanopsin gene but it fails to provide guidance in terms of its functional involvement in genus of disorder nor does it disclose a relationship to a condition associated with any of the disorder that could be treated by any therapeutic agent identified by the instant methods. Therefore, because an artisan does not know the function of melanopsin and does not know of any known direct relationship to a disease or condition, and artisan would not know how to use any identified compounds. Furthermore, for an artisan to use or make the instant method for its intended use, an artisan would have to determine the function of melanopsin in different disorder as et forth in claims (see page 15, para. 54) and if there are any disease or specific conditions associated with melanopsin. Therefore, given the act that an artisan would not know how to use the instant method for identifying an agent that modulates circadian rhythm. It is emphasized that the specification does not provide any specific guidance for the use of a method for identifying agents that treat any particular disease. The specification teaches that agents identified through the screening method of the

invention are potential therapeutics for use in a number of conditions including depression, Alzhemier's disease and jet lag (supra). It is noted that the function of melanopsin gene product has been speculated to be localized to the inner layer of the retina, within ganglion and amacrine cells (Beaule et al, Journal of Molecular Neuroscience, 2003, 73-89, page 75, col. 1, para 2) which is considered circadian photo receptor (abstract). However, post filing art summarized by the reference of Beaule et al (Journal of Molecular Neuroscience, 2003, 73-89) suggest melanopsin in itself is not necessary for circadian photoreception. Beaule states, " In fact it appears that within the photoreceptive system there is some degree of redundancy, each contributing in some way to photoic entrainment"(abstract). In addition, Kavakli et al (Mol Interv. 2002 Dec;2(8):484-92, art of record) while reviewing the role of melanopsin as a possible circadian photoreceptor states " Melanopsin knockout mice have recently been generated to analyze this hypothesis. The animals entrain normally to LD cycles, show phase shifting in response to short light pulses, and manifest normal photic induction of clock genes in the SCN. It appears, however, that under dim light, the magnitude of phase shifts is moderately reduced relative to wild-type animals. Assuming that this effect is not due to differences between mouse strain backgrounds, it appears that melanopsin either directly or indirectly plays a minor role in circadian photoreception"(page 488, col. 2, see melanopsin knockout mice section). It is noted that cited art show only marginal role of melanopsin gene in regulating circadian rhythm. However, art of record and the specification fail to establish this relationship to indicate that melanopsin in the sole gene responsible for circadian rhythm phase shift in any animal in response to any light pulse. In the instant case, claimed invention recite a phenotype, which may be partly related to melanopsin knockout given the unpredictability in the phenotype and influence of genetic background on phenotype an artisan for the specific reasons cited above it would have required undue experimentation for an artisan of skill to make use of the claimed invention. It is noted that specification does not provide any specific teaching regarding how individual symptoms are related specifically to any condition or type of agents, amount needed, dosage schedule and delivery route that would be used to identify the agent. An artisan

would have to perform undue experimentation to first establish a link between the transgenic knockout animal with a specific condition and then test various parameters using different type of agents, dosage and delivery route in order to reduce symptoms seen the transgenic animal of the invention. It is emphasized that modulation of circadian rhythm condition can be cause by a variety of mechanism that may or may not have any involvement of melanopsin gene. Given that the specification and art do not disclose an known disease or disorder causes by impaired melanopsin, an artisan would not know if the instant mice represent a model for genus of disorder that would be applicable to a disease or condition associated with plurality of different disorders. Furthermore, an artisan would not know if the any particular agent identified using the knock out mouse would be able to treat a disease symptom similar to those observed in the any other mammal. An artisan would have to do further experimentation to determine if the symptoms associated with the knockout as associated and therefore representative a disease. In view of foregoing discussion, it is apparent that any difference of symptom seen in the instant transgenic mouse cannot be generally associated to melanopsin 'circadian disorders. Therefore, an artisan would not know if the compounds identified by testing in the transgenic mouse of the invention would be effective for its intended use in the modulating circadian rhythm disorder as contemplated in the instant application.

In conclusion, in view of breadth of the claims and absence of a strong showing by applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions. The specification and prior art do not teach "any" transgenic mouse for the claimed method. An artisan of skill would have required undue experimentation to practice the method as claimed because the art of making nonhuman transgenic other then mice and phenotype was unpredictable at the time of filing of this application as supported by the observations in the art record.

Response to Arguments

Applicant's arguments filed January 8, 2007 have been fully considered but they are moot in view of new grounds of rejections. The instant response is directed to the extent it address the issues raised in previous office action. Applicants in their argument on page 6, second paragraph state that Beaule and Kavakli both refer to the melanopsin knock out studies by Ruby et al and Panda. Applicant assert that these two studies show that mice lacking functional melanopsin exhibit a significant attenuation of phase shift in response to light pulse during dark portion of an environmental dark/light cycle. Applicants then cite Ruby and their own post filing publication (Panda et al) to conclude that melanopsin plays a significant role in magnitude of photic response. Applicant also argue that Kavalki et al provide no explanation as to why the difference in phase shift observed in melanopsin knockout mice in two different studies would be due to difference in mouse strain background.

In response, it is emphasized that issue is not whether specification teaches a melanopsin knock out mice with slight phase shift in phase shift in response to LP. Examiner agrees with the applicants that both Beaule and Kavakli disclose melanopsin knock out mice showing significant lengthening of free running period when mice housed in constant light (see Beaule et al., page 75, col. 2, para. 3). However, applicant have not described Beaule et al also disclose that results from these experiments do not provide support for a critical role of melanopsin in normal photic entrainment. Beaule studied the role of melanopsin on circadian response to light and concludes, "hope of melanopsin to be a primary circadian photoreceptor in mammal has to date is not fulfilled. Rather current evidence suggests that there are multiple redundant photosensitive system capable of transmitting photoperiodic information to the circadian system (see Figure 10, page 85, col. 2, last para). In addition, Examiner has also cited additional art indicating that disruption of a given opsin gene may result in compensation by other opsins (Kumbalasiri et al Exp Eye Res. 2005; 81(4): 368-75). Taken together the observation by Beaule, Kumbalasiri et al and Kavakli it would be reasonable to state that phenotype seen in the transgenic knockout mouse of the

invention may be compensated by another gene. Further, art of record also teaches role of genetic background plays critical role in resulting phenotype of a knockout mouse. Further, in absence of any specific nexus between the phenotype to any specific condition or disorder associated with any such deletion of the melanopsin gene in the transgenic knockout mouse of the invention. An artisan would have to perform undue experimentation to make use of the transgenic knockout mouse for screening or other assay as contemplated by the specification.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 1-2, 4 rejected under 35 U.S.C. 103(a) as being unpatentable over Provencio et al (The Journal of Neuroscience, 2000, 20(2): 600-605), Capecchi (US patent no. 5,464,764, November 7, 1995) and Genebank number GenBank Accession Number AF_147789, dated 1/15/2000) is withdrawn in view of amendment to the claims.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph. D
Examiner, AU 1632

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER